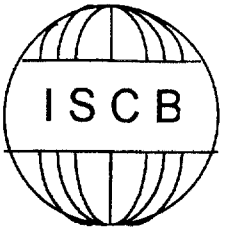


INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

Subcommittee on Regulatory Affairs

Secretary: Prof Stephen Senn, BA, MSc, PhD, CStat
Professor of Pharmaceutical and Health Statistics
Department of Epidemiology and Public Health, University College London,
1-19 Torrington Place, London WC1E 6BT, UK
Tel: +44 (0) 207 679 1698, Fax: +44 (0) 207 813 0280, Email: stephens@public-health.ucl.ac.uk

Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, rm. 1061,
Rockville, MD 20852.
USA

03 November 1999

Dear Sir or Madam,

Docket No. 97D-0433, CDER 9955. Draft Guidance for Industry on Average, Population, and Individual Approaches to Establishing Bioequivalence; Availability. Pages 48842-48843 [FR Doc.99-23228]

Please find enclosed a copy of comments on this document that have been prepared by the Subcommittee on Regulatory Affairs of the International Society for Clinical Biostatistics (ISCB) on behalf of the ISCB.

If you have any questions about this submission, please do not hesitate to contact me.

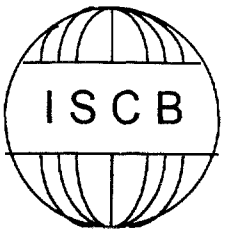
Yours sincerely

Prof Stephen Senn

Secretary, ISCB Subcommittee on Regulatory Affairs

97D-0433

C28



INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

Subcommittee on Regulatory Affairs

Comment on FDA Guidance for Industry: Average, Population, and Individual Approaches to Establishing Bioequivalence

Official reference: Docket No. 97D-0433, CDER 9955. Draft Guidance for Industry on Average, Population, and Individual Approaches to Establishing Bioequivalence; Availability. Pages 48842-48843 [FR Doc.99-23228]

Preamble: The International Society for Clinical Biostatistics
The International Society for Clinical Biostatistics (ISCB) was founded in 1978 to stimulate research into principles and methodology used in the design and analysis of clinical research and to increase the relevance of statistical theory to the real world of clinical medicine. Membership of the Society is open to all with an interest in biostatistics. The Society has a standing subcommittee on statistics in regulatory affairs and has commented on a number of international regulatory guidelines.

Comment on the Guidance for Industry
The ISCB welcomes the opportunity to comment on this document. If it is accepted that population and individual bioequivalence are important regulatory concerns then many of the recommendations seem sensible. However, the ISCB has some reservations as to the importance of these topics in the regulatory context as set out below.

1. In the view of the ISCB, bioequivalence is never an end in itself but merely a means to an end. By permitting registration on the basis of a reduced programme, it minimises the number of trials that need to be performed and the cost of development. This is in the public interest because i) it increases price competition in pharmaceuticals ii) it reduces experimentation in current patients iii) it frees resources for further innovation.
2. In the view of the Society the only universal regulatory standard is that of prescribability.
3. To the extent that additivity of treatment effects is assumed to apply, prescribability can be addressed by average bioavailability.
4. The further (beyond average bioavailability) requirement of population bioequivalence may only be an appropriate regulatory requirement if the route of administration of the test product differs from that of the reference. In particular, where the test product is delivered in a higher dose than the reference with the expectation that a lower fraction will be absorbed, thus producing equivalent average bioavailability, it is plausible that variances might differ. In other cases, where, for example, a simple generic copy of an existing formulation is being produced, it may be unnecessary to require population bioequivalence.
5. If, on the other hand, the concern about variability is due to worries about manufacturing quality, this is best seen as a quality control problem. Such concerns should usually be resolvable using in vitro studies.
6. It may be questioned as to whether individual bioequivalence should ever be required[1] as a condition of registration for the following reasons

I. If two formulations have the same marginal distributions, the probability that a naive patient will have a bioavailability within acceptable limits will be the same whichever formulation is used.
II. If two formulations have the same marginal distributions and a patient with a currently acceptable bioavailability is switched from one to the other, the probability that the patient will have a new acceptable bioavailability is higher than the probability for a naive patient being treated with either drug for the first time. Yet, this probability must be acceptable, else the drug could not be registered in the first place.
III. It is currently the case that two formulations of the same drug may be registered by free-standing dossiers. There are cases where different manufacturers have done this and compete in the same market. It is then possible for physicians to switch from one formulation to the other despite the fact that not even average bioequivalence has been proven. There is no contradiction in this provided that the key standard is seen as prescribability and it is accepted that prescribability may be demonstrated by one of two methods: either a full development or bioequivalence. This implies, however, that individual bioequivalence is not relevant to the requirements of registration. If it is to be addressed at all, it should be a labelling issue covering a further claim that manufacturers may wish to make.
IV. Either the situation that two formulations are equally prescribable but not switchable will not occur, in which case the proposed guidance will add unnecessary costs to bioequivalence, or it is possible that a formulation may be denied a license despite equal prescribability. In the latter case a formulation that would be equally acceptable to naive patients would be prevented from ever getting a license. However, the majority of patients at any one time might be naive patients for whom the requirement of switchability would be of no conceivable interest.

7. Thus, the position of the Society is that there should be no requirement to prove switchability unless a generic or other manufacturer wishes to make a particular claim that patients may be switched from existing formulations to new ones at no risk. Since such a claim would be a separate issue as to whether a drug should be registered or not, it would not make sense to have a single test for bioequivalence incorporating switchability. Prescribability would be established as a separate exercise and in order to make a further claim of switchability the sponsor would be required to show that the relevant component of variation was small.
8. The Society reserves its position, however, as to what exact form of statistical approach is indicated where, due to a change of route of administration, population bioequivalence might be a desirable goal. The technical properties of the FDA's proposal need more careful consideration and other possible approaches, for example using explicit loss functions, need to be considered also.

Reference:

1. Senn, S.J. In the blood: proposed new requirements for registering generic drugs. *Lancet*, **352**, 85-86, 1998.

DHL WORLDWIDE EXPRESS

Shipment Airwaybill

(Non negotiable)

4027918252

Quote this shipment number in an enquiry

ORIGIN: LHR

DESTINATION: GAI

1 From (Sender)

Account no: 130810847

Sender's name: PROF STEPHEN SENN

Sender's reference *first twelve characters will be shown on invoice*

UNIVERSITY COLLEGE LONDON
(EPIDEMIOLOGY & PUBLIC HEALTH)
1-19 TORRINGTON PLACE
LONDON

Postcode: WC1E 6BT

Phone/Fax/Telex: 0171 391 1680

2 To (Receiver)

FOOD AND DRUG ADMINISTRATION
5630 Fishers Lane
Rm 1061
Rockville

Postcode: MD 20852 USA

Contact person: THE MANAGER

Phone/Fax/Telex:

3 Shipment details

Not all payment and service options are available in all countries

Services

- [x] DOCUMENT
- [ ] WORLDWIDE PARCEL EXPRESS *all declarables*
- [ ] INTRA EC *(In free circulation)*
- [ ] DOMESTIC
- [ ] WORLDMAIL
- [ ] OTHER SERVICE ..... *specify*

Transport charges *If left blank sender pays transport charges*

- [x] Sender
- [ ] Cash/Cheque/Credit Card *For approved customers only*
- [ ] External Billing Agreement
- [ ] Transport Collect

Shipment insurance *see reverse*

- [ ] YES

Full description of contents

Documents

International Worldwide Parcel Express shipments only

Declared value:

Sender's VAT number:

Harmonised commodity code *if applies*:

Receiver's VAT No. or EIN/SSN:

Type of export: [ ] PERMANENT [ ] REPAIR/RETURN [ ] TEMPORARY

Destination duties/taxes *If left blank receiver pays duties/taxes*

[ ] Receiver [ ] Sender [ ] Other ..... *Specify destination approved account number*

4 Size and weight

No. of pieces	Weight
1	0.5 kg

Dimensions *cm L x W x H*

x x

VOLUMETRIC WEIGHT: kg

CODES	CHARGES Services
	Special
	Insurance
	Other/VAT

CURRENCY CODE	TOTAL

TRANSPORT COLLECT STICKER No.

PICKED UP BY

Route No. 151S

Time

Date

5 Sender's authorisation and signature

I/we agree that DHL's standard terms apply to this shipment and limit DHL's liability. The Warsaw Convention may also apply (see reverse). I/we understand that DHL does not transport cash or dangerous goods (see reverse).

Signature: P. Mg Stephen Senn

Date: 03/11/99

M 05/97 C